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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,449	11/17/2003	Ruben Laguens	42597-193226	9366

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,449	LAGUENS ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-97* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,10-16,19-39,43,44,51-66,69,71-73,76 and 79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 3,5-9,17,18,40-42,45-50,67,68,70,74,75,77,78 and 80-97.

DETAILED ACTION

Applicant's response filed on 10/26/06 has been acknowledged.

Election/Restrictions

Applicant's election of Group II (*method for inducing cardiomyogenesis by administering polynucleotide encoding VEGF*) in the reply filed on 10/26/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 3, 5-9,17-18, 40-42, 45-50, 67-68, 70, 74-75, 77-78 and 80-97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/26/06.

Claims 1-2, 4, 10-16, 19-39, 43-44, 51-66, 69, 71-73, 76 and 79 are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Claim Rejections - 35 USC § 112

Claims 1-2, 4, 10-16, 19-39, 43-44, 51-66, 69, 71-73, 76 and 79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature Of Invention

The instant invention relates to a method for inducing cardiomyogneesis by administering to a cell or tissue a polynucleotide encoding VEGF.

Breadth Of Claims And Guidance Provided in the Specification

The scope of invention as claimed encompasses method for inducing cardiomyogenesis in-vivo by administering a nucleic acid encoding any VEGF variant or an ex-vivo modified cell encoding any VEGF wherein via any and all routes of administration. The specification as filed fails to disclose that genetic modification any type of cell or tissue (i.e. non-cardiomyocytes) by a polynucleotide encoding any VEGF variant leads to cardiomyogenesis explicitly or implicitly as putatively claimed herein. In addition the specification as filed fails to disclose that genetic modification of cardiomyocytes with a polynucleotide encoding any VEGF variant induces mitosis or proliferation of cardiomyocytes.

State Of Art And Predictability

The scope of the instant invention encompasses genetic modification of a cell in-vivo, therefore the invention falls in the realm of gene therapy. The gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy (see Goncalves, Bioessays. 27(5):506-517, 2005; Juengst, BMJ, 326:1410-11, 2003; Check NATURE 422:7, 2003; Couzin et al, SCIENCE 307:1028, 2005; Wolf, NAT. BIOTECHNOL. 20, 768-769, 2002, Rosenberg et al, SCIENCE 287:1751, 2000; Anderson, NATURE 392:25-30, 1998; Touchette, NAT. MED. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success. The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. See delivery options for implementing myocardial gene transfer (Isner, *Nature* 415, 234-239, 2002).

In instant case the scope of invention as claimed encompasses a method for inducing cardiomyogenesis in-vivo by administering a nucleic acid encoding any VEGF variant or an ex-vivo modified cell encoding any VEGF wherein via any and all routes of administration. The specification as filed fails to disclose that genetic modification of any type of cell or tissue (i.e. non-cardiomyocytes) by a polynucleotide encoding any VEGF variant leads to cardiomyogenesis. In addition the specification as filed fails to disclose that even genetic modification of cardiomyocytes with a polynucleotide encoding any VEGF variant induces mitosis or proliferation of cardiomyocytes.

One of the greatest challenges facing gene therapy is the efficient transfer and stable expression of transgenes in appropriate tissues. Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells. In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes. Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in-vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets. In addition there exists an uncertainty about the degree to which a vector's genetic material may integrate into the host genome extends to most types of gene therapy trials. Scientists are also unsure how an insertion could

affect a patient, and worry cancer could occasionally be triggered, such as occurred various trials involving gene therapy (see Check Nature 422:7, 2003). Although, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals.

In instant case method for inducing cardiomyogenesis by transfecting any kind of target cells in-vivo via administering the polynucleotide encoding any variant of VEGF via any viral or non-viral vector, wherein the vector is administed via nay and all route os administration is not considered routine in the art and without sufficient evidence provided in the specification as filed the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4, 10-16, 19-39, 43-44, 51-66, 69, 71-73, 76 and 79 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Vale et al (Circ. 102:965-974, 2000).

The instant claim is drawn to a method for inducing cardiomyogenesis by administering a polynucleotide encoding a VEGF polypeptide.

Vale et al teaches a gene therapy method that assess efficacy of phVEGF(165) gene transfer in chronic myocardial ischemia. The cited art teaches that the NOGA electromechanical mapping (EMM) was prospectively performed in 13 consecutive patients with chronic myocardial ischemia before and 60 days after gene transfer (GTx) of naked DNA encoding for the 165-amino acid isoform of VEGF-1 ($phVEGF_{165}$), administered during surgery by direct myocardial injection. The cited art teaches that the present study constitute additional objective evidence that $phVEGF_{165}$ GTx augments perfusion of ischemic myocardium, and the results also support the notion that $phVEGF_{165}$ GTx successfully rescued foci of hibernating myocardium.

The cited art further teaches that the VEGF plasmid administered to all patients in the present study is a eukaryotic expression vector encoding the 165–amino acid isoform of the human VEGF gene transcriptionally regulated by the cytomegalovirus promoter/enhancer ($phVEGF_{165}$). The cited art further teaches that A left lateral minithoracotomy was used to expose the heart, after which direct myocardial GTx was performed with a 25-gauge needle under continuous transesophageal echocardiographic monitoring. A total dose of 250 μg (n=5) or 500 μg (n=8) was divided into 4 aliquots, each delivered in 2.0 mL of normal saline to the lateral, anterior, or septal LV wall. The injection sites were selected according to the areas of ischemia identified by prior NOGA and sestamibi imaging (see page 966 col.1-2).

The cited art further teaches that the foci of ischemic myocardium, identified by preserved viability associated with impaired LLS, ie, electromechanical uncoupling, were demonstrated in all patients before GTx. The cited art teaches that the mean LLS in areas of myocardial ischemia, improved significantly from 9.94±1.53% before $phVEGF_{165}$ GTx to 15.26±0.98% after $phVEGF_{165}$ GTx (P=0.004). In addition the area of ischemic myocardium was consequently reduced from 6.45±1.37 cm^2 before $phVEGF_{165}$ GTx to 0.95±0.41 cm^2 after GTx (P=0.001), see page 967 col. 2 and Table 2. The cited art further provided examples of NOGA maps showing septal, lateral, anterior, and

inferior ischemic zones before GTx with improvement after GTx are shown in panel A of Figures 1 through 5 (see pages 968-972).

The cited art further teaches the collated electrical and mechanical results of percutaneous EMM provide both an assessment of myocardial viability (ie, the presence of normal versus reduced voltage) and wall motion (presence of normal versus reduced fractional shortening). The cited art teaches that the analysis of LLS in areas of myocardial ischemia, documented marked improvement after GTx. Consequently, the area of ischemic myocardium was reduced to a statistically significant extent. Furthermore the corresponding NOGA maps likewise showed reduced evidence of ischemia after GTx. EMM provides separate assessments of viability (endocardial voltage recording) and function (LLS). Thus, those areas of the NOGA map that showed viable myocardium with impaired function before GTx versus viable myocardium with improved function after GTx support the notion that the defects that resolved on the SPECT scans constitute sites of hibernating myocardium that have been resuscitated. There reduction of ischemic myocardium *inherently* induces cardiomyogenesis cell proliferation and/or mitosis. It has been even well established that by confocal microscopy that 14 myocytes per million were in mitosis in control human hearts. A nearly 10-fold increase in this parameter was measured in end-stage ischemic heart disease (152 myocytes per million) and in idiopathic dilated cardiomyopathy (131 myocytes per million). Because the left ventricle contains 5.8 x 10(9) myocytes, these mitotic indices imply that 81.2 x 10(3), 882 x 10(3), and 760 x 10(3) myocytes were in mitosis in the entire ventricular myocardium of control hearts and hearts affected by ischemic and idiopathic dilated cardiomyopathy, respectively (Kajstura et al, Proc Natl Acad Sci U S A. 95(15):8801-5, 1998, see page 8803, fig-2, page 8904 col.1-2).

Furthermore it is well settled that routine optimization is not patentable, even if it results in significant improvements over the prior art. In support of this position, attention is directed to the decision in *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955): Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. In instant case the modification as claimed in the instant invention encompasses obvious variations over

cited prior art of record, which are well within the reach of one ordinary skilled in the art. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. In re Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52; In re Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In re Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; In re Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. In re Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; In re Normann et al., 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308; In re Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added). With regards to determining experimental parameters, such as time in culture, the court has held that "[d]iscovery of optimum value of result effective variable in known process is ordinarily within skill of art (*In re Boesch and Slaney*, 205 USPQ 215 (CCPA 1980). Thus given the broadest reasonable interpretation the invention as claimed is prima facie obvious if not anticipated in view of cited prior art of record.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is

571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
PRIMARY EXAMINER
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